(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 June 2004 (17.06.2004)

PCT

(10) International Publication Number
WO 2004/050022 A3

(51) International Patent Classification[7]: A61K 31/397, 31/40, 31/426, 31/445, C07D 205/04, 207/04, 277/04, 295/192

(21) International Application Number:
PCT/US2003/037825

(22) International Filing Date:
26 November 2003 (26.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/430,836 4 December 2002 (04.12.2002) US

(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DUFFY, Joseph, L.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **MATHVINK, Robert, J.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **WEBER, Ann, E.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **XU, Jinyou** [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with amended claims and statement*

(88) Date of publication of the international search report:
5 August 2004

Date of publication of the amended claims and statement:
30 September 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHENYLALANINE DERIVATIVES AS DIPEPTIDYL PEPTIDASE INHIBITORS FOR THE TREATMENT OR PREVENTION OF DIABETES

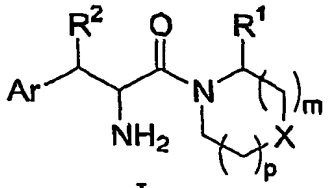
(57) Abstract: The present invention is directed to phenylalanine derivatives which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

WO 2004/050022 A3

AMENDED CLAIMS

[Received by the International Bureau on 18 August 2004 (18.08.04)]

1. A compound of structural formula I:



I

or a pharmaceutically acceptable salt thereof; wherein
each n is independently 0, 1, or 2;
m and p are independently 0 or 1;
q is 1 or 2;

X is CH_2, S, CHF, or CF_2;

Ar is phenyl, unsubstituted or substituted with one to five R^3 substituents;

R^1 is hydrogen;

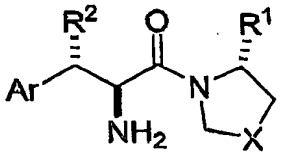
R^2 is selected from the group consisting of
C_{1-10} alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen or hydroxy,
C_{2-10} alkenyl, wherein alkenyl is unsubstituted or substituted with one to five substituents independently selected from halogen or hydroxy,
$(CH_2)_n$-aryl, wherein aryl is unsubstituted or substituted with one to five substituents independently selected hydroxy, halogen, CO_2H, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,
$(CH_2)_n$-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three substituents independently selected from hydroxy, halogen, CO_2H, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

[(tetrazol-5-yl)amino]carbonyl.

15. The compound of Claim 14 wherein R^3 is selected from the group consisting of:

fluoro,
chloro,
bromo,
trifluoromethyl,
trifluoromethoxy, and
methoxy.

16. The compound of Claim 1 of the structural formula Ij



(Ij)

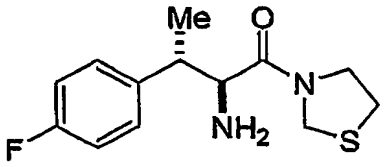
wherein X is CH_2, S, CHF, or CF_2;
Ar is phenyl, unsubstituted or substituted with one to five R^3 substituents;
R^1 is hydrogen;

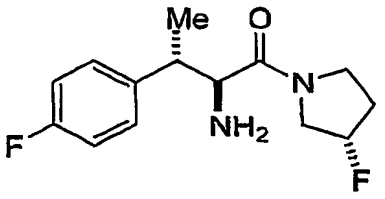
R^2 is selected from the group consisting of
C_{1-6} alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen or hydroxy,
$(CH_2)_n$-C_{3-6} cycloalkyl,
COOH,
$COOC_{1-6}$ alkyl, and
$CONR^4R^5$, wherein R^4 and R^5 are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, $(CH_2)_n$-phenyl, $(CH_2)_n$-C_{3-6} cycloalkyl, and C_{1-6} alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C_{1-6} alkyl, and C_{1-6}

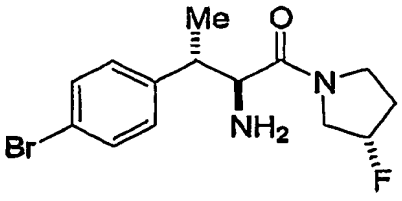
alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;
or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclic ring selected from pyrrolidine, piperidine, piperazine, and morpholine wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and

each R^3 is independently selected from the group consisting of:
halogen,
C_{1-6} alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens,
C_{1-6} alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,
phenyloxy, unsubstituted or substituted with one to three substituents independently selected from halogen and cyano, and
phenyl$(CH_2)_nCON(Me)$-, wherein phenyl is unsubstituted or substituted with one to three substituents independently selected from halogen, trifluoromethyl, and C_{1-4} alkyl.

17. The compound of Claim 16 of the structural formula selected from the group consisting of







Statement under Article 19(1)

Claims 1, 16 and 17 of the international application have been amended to exclude compounds disclosed in WO 03/002530 cited in the International Search Report . The present amendment does not introduce new matter and is fully suppported by Applicants' description. The present amendment has no impact on the description and the drawings of the international application.